

This new section will contain review articles that focus on a particular disease or public health policy. This month there are two public health reviews. The first, by Philippe G. Kestelyn & Emmett T. Cunningham Jr, deals with the ocular problems associated with HIV/AIDS. It is followed by a review, by John P. Whitcher, M. Srinivasan, & Madan P. Upadhyay, of the global problem presented by corneal blindness.

HIV/AIDS and blindness

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Nearly 34 million people are currently living with HIV/AIDS: ocular complications are common, affecting 50% to 75% of all such patients at some point during the course of their illness. Cytomegalovirus retinitis is by far the most frequent cause of vision loss in patients with AIDS. Although the prevalence of cytomegalovirus retinitis is decreasing in industrialized countries because of the widespread availability of highly active antiretroviral therapy, between 10% and 20% of HIV-infected patients worldwide can be expected to lose vision in one or both eyes as a result of ocular cytomegalovirus infection. Less frequent but important causes of bilateral vision loss in patients with HIV/AIDS include varicella zoster virus and herpes simplex virus retinitis, HIV-related ischaemic microvasculopathy, ocular syphilis, ocular tuberculosis, cryptococcal meningitis, and ocular toxic or allergic drug reactions. At present, most patients with HIV/AIDS in developing countries who lose their vision have a very limited life expectancy. As antiretroviral therapy makes its way to these countries, however, both life expectancy and the prevalence of blindness related to HIV/AIDS can be expected to increase dramatically.

Keywords: HIV infections/complications; Acquired immunodeficiency syndrome/complications; AIDS-related opportunistic infections/complications; Blindness/etiology (*source: MeSH*).

Mots clés: HIV, Infection/complication; SIDA/complication; Infections opportunistes liées SIDA/complication; Cécité/étiologie (*source: INSERM*).

Palabras clave: Infecciones por VIH/complicaciones; Síndrome de inmunodeficiencia adquirida/complicaciones; Infecciones oportunistas relacionadas con el SIDA/complicaciones; Ceguera/etiología (*fuentes: BIREME*).

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Introduction

It is difficult to assess the contribution of HIV/AIDS to blindness worldwide. Most studies on the prevalence of ocular complications in HIV/AIDS have been carried out in industrialized countries (1), while more than 90% of all HIV sufferers live in the developing world (2). Furthermore, there is

strong evidence that both the spectrum of ocular complications and their prevalence differ substantially between developing and industrialized countries (1). Taken together, these factors limit the validity of extrapolating the prevalence rates of ocular complications in North America and Europe to the more than 30 million HIV-infected patients living in sub-Saharan Africa, South Asia, and South-East Asia. Nevertheless, we have attempted to investigate the global importance of HIV-related blindness. Special attention has been given to those diseases that have the potential to affect both eyes, including cytomegalovirus (CMV) retinitis, acute retinal necrosis, the variant of acute retinal necrosis referred to as progressive outer retinal necrosis, HIV-related ischaemic microvasculopathy, ocular

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syphilis, ocular tuberculosis, cryptococcal meningitis, as well as ocular toxic or allergic drug reactions. Although other ocular disorders are observed commonly in HIV-positive patients, including herpes zoster ophthalmicus, ocular toxoplasmosis, Kaposi's sarcoma of the ocular adnexae, and conjunctival neoplasias, these tend to affect one eye only (1) and are therefore not considered in this review.

Cytomegalovirus retinitis

CMV retinitis tends to occur in advanced HIV infections, usually once the CD4+ T-cell count has fallen below 50 cells/ μ l. Before 1997, approximately 30% of patients with AIDS developed CMV retinitis (3). In industrialized countries, the incidence of CMV retinitis in patients with CD4+ T-cell counts of less than 50/ μ l was about 20% per year, and approximately 40% of patients with CMV retinitis developed bilateral eye disease (4). The introduction of HIV protease inhibitors in 1995 quickly led to the development of combination therapy, termed highly active antiretroviral therapy (HAART). As a result of HAART, many patients experienced a decline in HIV replication, a marked improvement in immune function, and an associated decline in morbidity and mortality caused by opportunistic infection. The number of cases of CMV retinitis also decreased by 55% to 95% (5). In a study performed at a single centre, data collected in 1995 before the introduction of HAART showed a 6.1% annual incidence of newly diagnosed cases of CMV retinitis among all HIV-positive patients, whereas the annual incidence of new cases in 1997 — after the introduction of HAART — was 1.2% (6). The combination of HAART and effective anti-CMV drugs, such as ganciclovir, foscarnet and cidofovir, has vastly improved the visual prognosis for patients with CMV retinitis, and has dramatically reduced the risk of developing bilateral blinding disease in the industrialized world.

Immune recovery uveitis occurs in patients with a history of CMV retinitis who experience immune reconstitution while on HAART. The prevalence of the disease among such patients varies from 18% to 63%, resulting in an overall incidence of 0.11/person-year to 0.83/person-year (7, 8). The primary clinical feature of immune recovery uveitis is vitreous inflammation, which can lead to the formation of cystoid macular oedema, an epiretinal membrane, and retinal neovascularization.

In the developing world, the prevalence of CMV retinitis seems to be lower. A comparison of reports from various centres in Africa has indicated that the overall prevalence of CMV retinitis in African patients with AIDS varied from 0% to 8.5% (9). In a recent study of a cohort of 200 West African patients with AIDS who were followed for 20 months, the incidence of CMV retinitis was 43/4000 person-months and the average survival time was 22 days (10). This corre-

sponded roughly to a point prevalence of 1.5%, which supported earlier data obtained in cross-sectional surveys (9). In Chennai, South India, an overall prevalence of CMV retinitis of 17% was seen in a series of 100 consecutive patients with HIV infection (11), whereas in a cross-sectional study of 150 HIV-positive patients from Thailand, the prevalence was 25% (12). CMV retinitis affected 25% of 445 HIV-infected patients in São Paulo, Brazil (13). These figures indicate that the prevalence of CMV retinitis varies from region to region and that between 5% and 25% of all HIV-infected patients in the developing world can be expected to develop this blinding disorder at some point during the course of their illness.

Progressive outer retinal necrosis and acute retinal necrosis

Non-CMV retinitis is a much less common cause of retinal infection in HIV/AIDS patients. Progressive outer retinal necrosis — a disease caused mainly by varicella zoster virus — is characterized by fulminant, progressive retinal necrosis with relatively little vitreous inflammation (14). Bilaterality is the rule, either at or soon after the onset of the disease. Severe visual loss and retinal detachment typically occur within a matter of weeks. Risk factors include a low CD4+ T-cell count and a recent or current cutaneous, cerebral or visceral herpes zoster infection. No data are currently available on the prevalence of progressive outer retinal necrosis in the developing world. It has been reported in African patients (15), perhaps not surprisingly since dermatomal herpes zoster infection, one of the risk factors for this necrosis, is very common among HIV-positive patients in Africa (16).

The presentation of acute retinal necrosis in patients with AIDS is similar to that in immunocompetent individuals, and is characterized by vitreous inflammation, retinitis and retinal vasculitis. Most cases of acute retinal necrosis are attributable to varicella zoster virus, although herpes simplex virus may produce an identical clinical picture, often following or in association with viral encephalitis. Like progressive outer retinal necrosis, acute retinal necrosis develops rapidly, often leads to blindness, and frequently affects both eyes (14). Cases of acute retinal necrosis have been reported from Africa (17), Brazil (13), and India (11, 18), but the prevalence of both types of retinal necrosis among HIV-positive patients in the developing world is unknown.

HIV-related ischaemic maculopathy

Retinal cotton-wool spots, the hallmark of HIV retinopathy, are probably the most common ocular manifestation of HIV infection (1), occurring in about 50% of patients with HIV/AIDS (18). While there seems to be no difference in the prevalence of HIV retinopathy between African and North American HIV-infected patients (17), reports from Brazil

(13) and India (11) suggest somewhat lower prevalences of 1% and 8% respectively. The reasons for such differences are unknown.

Like CMV retinitis, HIV retinopathy tends to occur in advanced HIV disease, usually once the CD4+ T-cell count has fallen below 50 cells/ μ l (19). Although common, such microvascular changes only cause vision loss when they affect the perifoveal capillaries and cause ischaemic maculopathy (17, 20–22). The etiology of HIV retinopathy is obscure but the fact that it rarely develops after successful HAART indicates that either HIV itself and/or the host response to retroviral infection may play a role (23).

Ocular syphilis

Syphilis is the commonest bacterial intraocular infection in HIV-infected patients (1, 24). Vision loss in patients with syphilis occurs most frequently as a result of either uveitis or optic nerve disease, which may manifest itself as papillitis, perineuritis or retrobulbar optic neuropathy, although uveitis appears to be the most common complication (24). Several case reports and case series have described syphilitic ocular involvement in mainly North American HIV-positive patients (24, 25). Virtually no information is available on the prevalence or presentation of ocular syphilis in HIV-infected patients in sub-Saharan Africa and Asia, although a 1% prevalence of syphilitic uveitis was reported among HIV-positive patients in Brazil (13). Several seroepidemiological surveys have demonstrated a high prevalence of active syphilis among HIV-infected patients in sub-Saharan Africa (26). It is therefore to be expected that complications leading to blindness attributable to syphilis occur in Africa, and indeed in other developing countries, but are probably underdiagnosed.

Ocular tuberculosis

Tuberculosis is the single most important HIV-related opportunistic infection in developing countries (27). In Africa, between 30% and 50% of adults harbour latent tuberculosis that may be reactivated in the presence of HIV infection (28, 29). It is unclear whether the increased prevalence of tuberculosis in HIV-infected patients is associated with a significant rise in ocular morbidity. Reports from North America of extraocular tuberculosis in patients with AIDS make no mention of ocular involvement (30). In Malawi, an examination of 68 HIV-positive patients with tuberculosis revealed one patient with bilateral choroiditis and a second with unilateral necrotic retinitis (31). An examination of 32 HIV-positive Rwandan patients with tuberculosis disclosed a case of vision loss caused by bilateral, disseminated choroidal invasion in a severely ill patient who died shortly afterwards (15). However, given the huge number of

patients with both HIV/AIDS and active tuberculosis in developing countries it is probable that ocular complications of tuberculosis occur more frequently than has been recognized (32).

Ocular complications of cryptococcal meningitis

The most common life-threatening fungal pathogen that affects patients with AIDS is *Cryptococcus neoformans*. The prevalence of cryptococcal disease in different series of patients with AIDS from North America ranged from 2% to 9% (33, 34). Cryptococcal meningitis is more common in developing countries, however, probably because of a high prevalence of *C. neoformans*. A study in Bangalore, South India, of 100 HIV-positive patients with neurological disorders showed that the most common cause of neurological disease was cryptococcal meningitis, affecting 46.3% of all patients (35). In a rural, population-based cohort study on the causes of death due to HIV infection in Uganda, cryptococcal meningitis accounted for 13% of all deaths, and was the third most common cause of death after wasting syndrome and chronic diarrhoea (36). If left untreated, cryptococcal meningitis is always fatal. In a series of African patients, successful treatment resulted in a median survival time of 162 days but loss of vision developed in up to 5% of the patients because of either optic neuropathy or cortical blindness (37).

Drug reactions

Stevens–Johnson syndrome is part of a spectrum of skin and mucous membrane diseases caused by a hypersensitivity reaction to various drugs or toxins, of which sulfa drugs are the most common (38). The conjunctiva is frequently involved and there may be vision loss because of the combined effects of decreased tear production and fornical foreshortening with trichiasis, which together result in corneal scarring. A study in Kenya demonstrated that tuberculosis patients infected with HIV had an increased risk of developing hypersensitivity reactions when treated with thiacetazone (39). A report from Malawi showed that 75% of patients admitted with Stevens–Johnson syndrome were HIV-positive (40). Many of these patients had taken sulfadoxine-pyrimethamine, an antimalarial drug widely used in Africa. Other drugs associated with Stevens–Johnson syndrome in HIV-positive patients include β -lactam antibiotics, phenytoin, and nevirapine (41).

Both cidofovir (used to treat CMV infection) and rifabutin (used both prophylactically and in the treatment of *Mycobacterium avium* intracellular infection) can cause a severe vision-threatening anterior uveitis in HIV-infected patients (42). Although these drugs are used routinely in North America and Europe, their use has been limited in developing countries.

Discussion

This overview indicates that we need much better data on the prevalence and incidence of the complications of HIV infection which may lead to blindness in different parts of the world. However, the available evidence suggests that at present the main cause of blindness associated with HIV infection is bilateral CMV retinitis, which, ironically, has now become relatively uncommon in North America and Europe because of the availability of a number of effective anti-CMV medications and, more recently, the introduction of HAART.

Although the vast majority of HIV-infected patients — and thus the majority of blindness resulting from HIV/AIDS — are in the developing world, CMV retinitis seems to have been less prevalent in developing than in industrialized countries, at least prior to the advent of HAART. This lower prevalence is probably not a result of lower incidence, but is due to the very short survival times of patients in these regions once they develop CMV retinitis (1, 9). This is illustrated in a study of a cohort of African AIDS patients: the annual incidence of CMV retinitis was almost 13%, but their mean survival time was only 22 days (10). This is in sharp contrast to the survival times of 6 to 12 months seen among similar patients in industrialized countries before the introduction of HAART (1). These findings have important implications. As single antiretroviral agents become more widely available in the developing world, life expectancy may increase but immune reconstitution will not. The prevalence of CMV retinitis can be expected to increase, therefore, unless full HAART becomes widely available. Moreover, if the introduction of antiretroviral therapy is not matched by the introduction of effective anti-CMV medications and by the expertise needed to use them there will probably be an epidemic of blindness resulting from CMV retinitis in developing countries. Similarly, a number of the other opportunistic diseases that are less common than CMV retinitis, including progressive

outer retinal necrosis, cryptococcal meningitis, and disseminated choroidal tuberculosis, are equally associated with poor survival rates. This is why few blind AIDS patients are observed in cross-sectional surveys conducted in the developing world, although it is probable that hundreds of thousands of AIDS victims spend the last weeks of their lives in darkness. Increased survival through improved diagnosis and treatment of such opportunistic infections can be expected to increase the prevalence of blindness in patients with AIDS. Cryptococcal meningitis, for example, is one of the leading opportunistic infections in the developing world. If adequate treatment had been universally available in 1999, some 200 000 patients with AIDS could have been treated for cryptococcal meningitis during that year, assuming that *C. neoformans* was responsible for 10% of the 2 million reported AIDS deaths in developing countries. Approximately 5%, i.e. 10 000, of these patients would have lost their eyesight and spent the last six months of their lives either partially or totally blind.

It would be too simple to assume that the impact of HIV infection on blindness can be fully described in terms of the direct ocular complications that arise in HIV-infected patients. HIV/AIDS has such an overwhelming impact on social and economic structures that its effects are felt in much less obvious ways. So far the epidemic has left 13.2 million orphans (2). In African countries where HIV/AIDS is endemic, traditional family structures can no longer cope with the huge number of orphans generated by the epidemic. There is evidence from UNICEF that AIDS orphans are at increased risk of malnutrition, illness, abuse, and sexual exploitation. It is highly probable that such orphans are also at increased risk of developing vitamin A deficiency and xerophthalmia — whether they are HIV-positive or not. ■

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Résumé

VIH/SIDA et cécité

Près de 34 millions de personnes vivent actuellement avec le VIH/SIDA : les complications oculaires sont courantes et touchent 50 à 75 % de ces patients à un moment ou à un autre de l'évolution de la maladie. La rétinite à cytomégalovirus est de loin la cause la plus fréquente de la perte de vision chez les malades atteints de SIDA et, bien que sa prévalence soit en diminution dans les pays industrialisés grâce à l'accès à des traitements antirétroviraux très efficaces, il est prévisible qu'à l'échelle mondiale l'infection oculaire par le cytomégalovirus entraînera une perte de vision unilatérale ou bilatérale chez 10 à 20 % des personnes infectées par le VIH. Parmi les causes importantes mais moins fréquentes de perte de vision bilatérale chez les

personnes atteintes de VIH/SIDA figurent la rétinite due au virus varicelle-zona ou au virus de l'herpès, la microvasculopathie ischémique liée au VIH, la syphilis oculaire, la tuberculose oculaire, la méningite à *Cryptococcus* et les réactions oculaires toxiques ou allergiques consécutives à la prise de médicaments. Actuellement, la plupart des personnes atteintes de VIH/SIDA dans les pays en développement et qui perdent la vue ont une espérance de vie très réduite. A mesure que les traitements antirétroviraux progresseront dans ces pays, on peut prévoir que l'espérance de vie s'améliorera, mais qu'en même temps on assistera à une augmentation considérable de la prévalence de la cécité associée au VIH/SIDA.

Resumen

VIH/SIDA y ceguera

Casi 34 millones de personas viven actualmente con el VIH/SIDA: las complicaciones oculares son frecuentes, pues afectan al 50%–75% de esos pacientes en algún momento de la evolución de su enfermedad. La retinitis por citomegalovirus es, con mucho, la causa más frecuente de pérdida de visión entre los enfermos de SIDA. Aunque la prevalencia de la retinitis citomegalovírica está disminuyendo en los países industrializados como consecuencia de la amplia disponibilidad de antirretrovíricos de gran potencia, se calcula que entre un 10% y un 20% de los pacientes infectados por el VIH en todo el mundo pierden la visión en uno o ambos ojos de resultas de una infección ocular por citomegalovirus. Otras causas importantes aunque menos frecuentes de

pérdida de visión bilateral en los pacientes con VIH/SIDA son las retinitis causadas por los virus varicela-zoster y herpes simplex, la microvasculopatía isquémica asociada al VIH, la sífilis ocular, la tuberculosis ocular, la meningitis criptocócica y las reacciones oculares de origen tóxico o por alergia a medicamentos. En la actualidad, la mayoría de los pacientes con VIH/SIDA de los países en desarrollo que pierden la visión tienen una esperanza de vida muy limitada. Sin embargo, cabe prever que a medida que el tratamiento antirretrovírico penetra en esos países, tanto la esperanza de vida como la prevalencia de la ceguera asociada al VIH/SIDA aumentarán considerablemente.

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